EYE CHANGES IN RELATIONSHIP TO DISORDERS OF THYROID FUNCTION*

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EYE changes associated with disorders of thyroid function are seen both by thyroid clinicians and by ophthalmologists, but their points of view regarding them differ. The thyroid clinician looks upon such events as serious complications or casualties of treatment of the thyroid disorder for which he feels responsible although actually he may not be and thinks of them in terms of disturbed endocrine physiology; the ophthalmologist must consider them primarily as problems in therapy, sometimes immediate and urgent. The relationship between the thyroid disorder and the eye change must be subordinated at that point to the immediate problem of protecting the involved eye. In a casual or infrequent association with Graves' disease, the clinician is likely to be unimpressed by the problems of the eye changes because they will be encountered infrequently—for we must remember that a very large number of patients with toxic goiter never have noticeable eye changes regardless of changes in thyroid function; but to the thyroid clinician, who sees a large group of thyroid patients, and especially to the ophthalmologist, toward whom the patients with eye disorders gravitate, the problem is important and pressing. The fact that the incidence is low does not minimize in the least its seriousness. The surgeon is concerned over the development of hypothyroidism, recurrent nerve injury, and hypoparathyroidism, yet none of these complications is really comparable with severe ocular disfigurement, disability or loss of vision. It seems to me that so long as these threats exist the clinician handling disorders of thyroid function must do everything he can to avoid or prevent this complication, infrequent as it may be.

What *is* the actual incidence of these eye changes? Before answering this question, perhaps we should discuss what is meant by "eye changes" and present some facts regarding the type of thyroid disorder in which

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they occur. These eye changes have certain characteristics which I believe occur in association with no other disturbance. They are seen in patients who at some time or other suffer from Graves' disease. The goiter in this disease is a diffusely hyperplastic toxic gland. In our experience the condition is rarely, if ever, associated with toxic nodular goiter. Therefore, when eye changes are found associated with definite nodular goiter investigation should be conducted along other lines, especially if there is unilateral or asymmetrical exophthalmos. Usually exophthalmos is associated with perfectly definite evidence of hyperthyroidism and seems roughly in proportion to its degree of severity. Thus it is that one has come to be synonymous with the other in the general clinical view. But actually, although there is this close relationship between exophthalmos and hyperthyroidism, the two co-exist but not in any clear-cut *direct* cause-and-effect relationship. The physiological mechanism undoubtedly involves other structures, notably the pituitary, but this mechanism is not yet well understood and I shall concern myself with the clinical manifestations only.

The eye changes, as we look at the patients, are many and varied but we have come to think of them in general, as falling roughly into two categories, those with relatively simple disorders of the lid opening and closing mechanism in which the problem is largely cosmetic and seldom serious; and those which are serious because of infiltration of the orbital contents with edema and cells which ultimately may result in fibrous fixation of the globe. This may be complicated further by proptosis and "papilledema," so that the threat to normal eye function and possibly vision is considerable. Whether the mechanism of production of these two types of eye changes is fundamentally the same, I shall not consider at this time. There seems to be no sharp dividing line between the two, clinically, for we see those which show only mild lid spasm at one extreme, and extensive infiltration with severe spasm at the other. There are varying degrees of both in-between. I shall ask you to think of them respectively for the time being simply as "not severe" or "severe" so that we may get some idea of the incidence of the really severe eye changes which are the ones which incapacitate eye motion or threaten vision.

In a study of the results of the surgical treatment in 615 cases of toxic goiter made five years or longer after operation, there were twenty-one patients rendered euthyroid and one with persistent hyper-

thyroidism who were found to have had eye changes before operation that persisted or who developed eye changes after operation sufficiently conspicuous and important so that they were segregated for study. There were three in this group who would be classified as having *severe* eye changes, that is, who had some eye disability persisting five years or longer following thyroid operation. I believe that this reflects fairly accurately the incidence of severe eye changes following the surgical treatment of Graves' disease. It is about 0.5 per cent to 1 per cent. It is interesting and significant that at the time the study was made, all of the eye changes in this group had become stable. There was no loss of vision and plastic operations were performed on the lids and muscles of fourteen out of the twenty-two cases, largely for cosmetic reasons. The eye changes had become stationary in varying periods of time—from a few months to upwards of ten years.

Another group of 115 patients showing eye changes associated with thyroid disorders, treated during a ten year period, has been studied somewhat more carefully with respect to the fluctuations in thyroid function and these I shall attempt to summarize. This group does not include all the eye changes that occurred during that time but it does include very nearly all the severe ones from which we may again roughly estimate the incidence.

Of the 115 cases, fifteen have been classified as severe (see Tables I and II) which constitute an incidence of about 1 per cent of the total toxic goiter patients *treated*. By far the majority of these patients were treated by partial thyroidectomy for they occurred during the ten year period immediately preceding the introduction of thyroid-inhibiting drugs. Of the 115, all but nine were treated by partial thyroidectomy. Of these nine, seven received no specific thyroid treatment and two were given radiotherapy to the gland. One of the latter, a man aged fifty was the only patient in the group who required enucleation (of one eye). It seems to me that other features besides the age and sex of this patient are worth noting. His presenting symptoms were those related to his eyes, particularly tearing and fullness of the right eye for six weeks, with diplopia and a feeling of pressure over that eye. There was a soft fullness, the globe was described as "bluish" and there was chemosis and dilatation of the conjunctival vessels. His measurements were right eye 26, left 21.5, and he showed lagophthalmos. He had the signs and symptoms of only *slight* thyrotoxicosis and his B.M.R. was

SEVERE EYE CHANGES ASSOCIATED WITH CHANGES IN THYROID FUNCTION FOLLOWING SURGERY AND RADIOTHERAPY

TABLE I—MEN

	Eye Changes at Onset of Treatment		*Clinical Estimate of Thyroid Function Before Treatment*	*RX.*	*Eye Changes During and After RX. of Thyroid*	*Eye Result After RX. of Thyroid*
	Age	*Degree*				
1. L.F.	18	R=L*	Normal - mild (plus 5%)	Op.	Eyes worse as BMR fell R>L.	5 yrs.: worse than before operation and L>R (Euthyroid) 7 yrs.: eyes (prominent) R=L stationary (Euthyroid).
2. L.L.	39	R=L	Moderate (plus 56%)	Op.	Right eye became worse and severe as BMR fell (—28%)	5 yrs.: rt. eye severe (Euthyroid). 8 yrs.: eyes seemed *normal* (Euthyroid).
3. D.H.	40	R>L*	Mild (plus 20%)	Op.	Eyes worse as BMR fell.	5 yrs.: stationary without disability. (Euthyroid). 19 yrs.: unchanged (Euthyroid).
4. J.R.	43	R=L*	Mild (plus 18%)	Op.	Eyes much worse as BMR fell.	5 yrs.: stationary. Improved with plastic lid operations (Euthyroid). 11 yrs.: unchanged (Euthyroid).
5. J.M.	49	R=L*	Moderate (plus 57%)	Op.	Eyes worse as BMR fell. Very bad 4 to 5 mos. after operation.	2 yrs.: improved and stationary (Euthyroid). (Lid plastic operation done then with improvement). 4 yrs.: stationary (Euthyroid). Died 4 yrs. plus.
6. J.G.	50	R>L*	Mild (plus 31%)	X.	Rt. eye grew worse under x-ray Rx. without much change in thyroid function.	3 mos.: enucleation rt. eye (mild hyperthyroid). Lt. eye involved but less severely. 2 yrs.: lt. eye improved (Euthyroid). 7 yrs.: lt. eye slightly prominent—no disability (Euthyroid).

*—Showed increasing ocular disability the result of infiltrative or infiltrative combined with spastic changes.

X—X-ray.

SEVERE EYE CHANGES ASSOCIATED WITH CHANGES IN THYROID FUNCTION FOLLOWING SURGERY AND RADIOTHERAPY

TABLE II—WOMEN

	Eye Changes at Onset of Treatment		*Clinical Estimate of Thyroid Function Before Treatment*	*RX.*	*Eye Changes During and After RX. of Thyroid*	*Eye Result After RX. of Thyroid*
	Age	*Degree*				
1. M.P.	24	R>L	Very mild (plus 6%)	Op.	Eyes worse as BMR fell.	1 yr.: worse than before Rx. (hypothyroid) 12 yrs.: eyes "normal" (euthyroid on thyroid)
2. E.F.	33	R=L*	Moderate (plus 39%)	Op.	Eyes worse as BMR fell.	14 mos.: stationary—severe (Euthyroid) 6 yrs.: stationary—severe (Euthyroid) (6 mos. pregnant).
3. M.W.	33	None*	Mild (plus 31%)	Op.	Severe bilat. infiltrative changes as BMR fell.	2 yrs.: stationary—severe (Euthyroid) No further follow-up.
4. G.S.	33	R>L*	Mild (plus 33%)	Op.	Unchanged—severe. Eyes prolapse.	12 yrs.: stationary—severe (Euthyroid) Eyes prolapsable.
5. M.D.	40	L>R*	Very mild (plus 15%)	X.	Rt. eye worse as BMR fell.	4 yrs.: rt. eye stationary — severe. (Euthyroid)
6. J.B.	42	None*	Mild (no record)	Op.	Eye worse as BMR fell.	3 yrs.: stationary—severe, R=L. (Euthyroid) Lost to follow-up.
7. E.H.	44	R=L*	Severe (plus 81%)	Op.	Eyes much worse as BMR fell.	9½ yrs.: stationary—seemed improved with thyroid and myomectomy (Euthyroid)
8. M.D.	47	R=L*	Moderate (plus 35%)	Op.	No change for 9 yrs then L>R.	9 yrs. 3 mos.: seemed improved with thyroid (Euthyroid) 24 yrs.: stationary *R>L* without symptoms (Euthyroid)
9. L.D.	55	R=L*	Mild (plus 68%)	Op.	Eyes worse after op. with corneal ulcer.	2 mos.: improved with bilateral plastic lid operations. 1 yr.: stationary—improved (Euthyroid) Lost to follow-up.

*—Showed increasing ocular disability the result of infiltrative or infiltrative combined with spastic changes.

X—X-ray.

plus 31 per cent. Following radiotherapy to the gland, the exophthalmos progressed on the right side and after exploration and partial orbital decompression and formation of lid adhesions, it was necessary to enucleate the right eye about three months after admission. Two years later he reported that he had seen no doctors during the preceding year, had simply applied cold compresses to the other eye three times a day, and that this eye was very much improved. He had no tremor or palpitation and had gained 15 pounds. I have almost come to the conclusion that this is the ideal form of therapy. In any event, time is a prime ingredient.

Two patients in this group, both women—aged thirty-three and forty-one respectively, had no eye signs or symptoms whatever prior to the institution of treatment for thyrotoxicosis. The thyroid disease was quite mild in both cases. On iodine and radiotherapy, the basal metabolism of the first fell to plus 18 per cent. She felt "a pressure" behind her eyes but no eye changes were noted. A month later her basal metabolism rose to plus 47 per cent and she was given iodine in preparation for operation. The metabolic rate fell to plus 27 per cent. The evidence for hyperthyroidism throughout (except the elevation of the B.M.R.) was largely subjective. After operation, the basal metabolism fell to plus 2 per cent and within a month of operation, her eyes were puffy, she complained of photophobia, and tearing. Four months later, she was euthyroid with a basal metabolism of plus 2 per cent but her eyes were very much worse—including limitation of rotation and spasm of the lid levators. Operation was suggested to protect the corneae but was refused. Four years later, the condition was somewhat improved and stationary. She was euthyroid (plus 2 per cent).

The course of the second case was very similar. She became moderately hypothyroid after operation during which interval her eyes grew worse. An unsuccessful plastic lid operation was performed on one eye two years after operation by which time the eyes seemed to have become stationary. They remained that way as long as she was followed (up to three years after operation) with definitely impaired function. She was euthyroid at that time (minus 9 per cent).

I should like to be able to present many other individual cases in detail, especially the more severe ones, because close study of these is far more instructive from a practical standpoint than a statistical analysis of such a complex subject. This is obviously impossible, however, and

I shall have to try to present the overall picture as well as I can by emphasizing what seem to be the significant features.

Let us look at the fifteen severe cases first. To recapitulate: All had toxic diffuse glands. Six of the fifteen were men. Of these, five were aged thirty-nine to fifty. The other was aged eighteen. Of the nine women, the ages were between thirty-three and fifty-five. Of all fifteen, ten were between the ages of twenty-nine and fifty-five.

An estimate of the thyroid function at the time the initial eye changes were noted reveals that nine were considered only mildly hyperthyroid, five were moderately toxic and one was severely toxic.

An estimate of thyroid function during and after treatment indicates that function became normal promptly in nine patients and remained so, and that mild hypothyroidism developed in two. In another, there was little apparent change, but this is the patient requiring enucleation. One patient, who seemed really normal before operation except for his eyes, became hyperthyroid a short time after operation but meantime his eyes grew alarmingly worse. He was given radiotherapy to the gland with very little effect. Sometime later, his thyroid function reverted to normal apparently spontaneously. His eyes remained bad and at five years, they were worse than before operation. At seven years, they were both still prominent but satisfactory, about equal, and causing no disability. He was euthyroid.

Of the eleven who became normal or hypothyroid after treatment, the eyes grew worse in a relatively short period of time in nine. In the other two, the eye changes did not develop for five and nine years respectively. One of these became hypothyroid after operation without any eye changes developing immediately. He slowly reverted to normal function without therapy and at five years his B.M.R. was plus 1 per cent. At that point, aged forty-four, he developed severe exophthalmos in the right eye with diplopia but three years later his eyes appeared normal and caused no disability. He was euthyroid. The second, a woman aged forty-seven, with moderate symmetrical exophthalmos became euthyroid after operation and remained so for nine years, then at age fifty-six developed marked prominence of the left eye without disability. Her B.M.R. at that time was plus 12 per cent although clinically she seemed somewhat hypothyroid. On thyroid she improved. Three months later her eyes appeared normal and remained so. Since that time we have seen one other patient in whom this sequence of

events was similar to that of the preceding cases. At age 37, this patient showed mild asymmetrical exophthalmos with hyperthyroidism (B.M.R. plus 45 per cent). Thyroidectomy was performed and she became euthyroid without any change in her eyes immediately post-operatively. Eleven years later at age forty-eight, while still euthyroid (plus 5 per cent) but very obese, she developed severe, acute, bilateral, alarming exophthalmos which responded rapidly to thyroid administration. (Her acute signs and symptoms have disappeared but tend to recur if she discontinues thyroid.)

It will be noted that thirteen of the fifteen patients with severe eye symptoms in this group showed evidence of infiltrative changes in the orbits by the presence of diplopia, limited motions of the globe, resistance to its attempted reduction, frequent evidence of peri-orbital edema and associated acute signs of conjunctival congestion. Eye symptoms were complained of at times even before the eye signs became apparent: a feeling of fullness or pressure behind or "on top of the eye ball," "visual discomfort," "pain in the eye," burning or smarting and lacrimation.

In the remainder of the 115 cases of eye disturbances studied, the changes were characterized by an absence of the signs and symptoms of infiltration seen so frequently in the severe group. The changes seemed rather to be disturbances of innervation of smooth muscle components of the lid opening and closing mechanism and there was a far greater tendency toward improvement of the eye condition as the hyperthyroidism came under control. Fifteen of these patients could be classified as normal in appearance and function after varying intervals of time from a month or two to ten years after operation (or other therapy), forty-two were definitely improved and thirty-nine were unchanged. (The cases that progressed under treatment were the ones included in the severe group.) The two groups have at least one thing in common; the eye changes tend to become stationary after varying periods of time whether they advance or regress, and a certain number of them do not change at all with fluctuations in thyroid function.

The seven patients who showed eye changes and who received *no* therapy affecting thyroid function, form rather an interesting group. These patients were sent, or presented themselves, to the clinic with eye changes which showed the simpler, less severe types. Five of these patients were either euthyroid at the time of the initial eye change or

had extremely mild and equivocal symptoms of hyperthyroidism but often a history of some kind of functional thyroid disorder. One of the patients was quite hypothyroid. One of the patients had a B.M.R. of plus 50 per cent but clinically the evidence of hyperthyroidism was not striking. In this patient, after a period of nine years, there was "spontaneous" remission to a frankly euthyroid state (minus 7 per cent). At eleven years, her eyes improved and appeared normal. She is one patient at least in whom we think there might have been an actual diminution of 3 mm. in the proptosis. There was unilateral exophthalmos in five of the seven patients. In the other two, it was bilateral and symmetrical. Initial studies were made to rule out other causes of unilateral exophthalmos. The subsequent courses, however, suggested quite strongly that these were of the thyroid type in four out of the five at least, because in three of them the eyes became normal, and in the fourth the eye which was exophthalmic initially, became normal and the other eye became prominent. In the fifth case, there was no change during a short follow-up interval. Of the two bilateral cases, one improved bilaterally and the other showed regression of one eye to normal, the other remaining prominent. The ages of these patients were twenty-eight to thirty-eight and all were women.

In some ways these patients resemble the three severe cases discussed earlier who had delayed eye changes at a time when they were euthyroid and had been so for many years. The patients with the delayed *severe* eye changes were all in the older age groups, however, and this may be of significance.

Out of this rather confusing mass of data, we set ourselves the task of trying to discover whether there were any clues which would be of help in spotting among those patients who came under our observation, any who might be expected to develop severe eye changes during or after treatment. One thing seemed quite certain: if such cases could be spotted, operation should be avoided if possible for we had found that the majority of the severe eye changes developed quite rapidly following partial thyroidectomy. This was interpreted as an abrupt and perhaps irreversible upset in the physiological balance which had maintained the various components of eye motion as nearly normal as possible under the abnormal conditions of hormone secretion in the thyroid, pituitary and possibly other glands. It was felt that the same result might be expected to occur following any form of therapy which acted

relatively rapidly and "irreversibly," as for example radioactive iodine. Realizing that the disease was self-limited, it followed that if the progression of the exophthalmos could be prevented and the eye protected during the often protracted period of change, the major problem might be solved and we might no longer have reason to fear this complication.

If then we further summarize and bring together those features of the data which I have attempted to present which seem to be pertinent, I think we do come up with some characteristics of this disorder significant enough clinically that are worth looking for in patients with definite or suspected Graves' disease.

1. *Age:* The majority of the patients who developed severe eye changes were between the ages of thirty-nine and fifty-five, that is *older* patients.

2. *Sex:* A higher proportion of men within that age group developed severe eye changes than develop Graves' disease as compared to women. Therefore look out for the older men with eye changes.

3. *Thyroid function at the time of initial eye change:* The majority of the cases were considered only mildly toxic or even normal and often remained so as the eye signs developed out of proportion to the *clinical* evidence of hyperthyroidism. This seemed to hold true even in patients whose basal metabolism tests were reported elevated. In other words, there seemed to be a tendency in general for the eye changes to develop early and out of proportion to the degree of hyperthyroidism which one usually associates with such severe exophthalmos. It is this group of patients who, because of the severe exophthalmos, may be operated upon inadvisably on the assumption that the exophthalmos is an expression of both the presence and the *degree* of hyperthyroidism.

4. Of the significant early signs and symptoms, lid-fullness, lacrimation, and a sense of fullness or pressure in the eye, at times with diplopia, seemed of particular importance. In asymmetries of the eyes it is most important to try to determine whether the asymmetry is due to infiltrative changes within the orbit (resistance to attempted reduction of the globe, occasional palpable lateral recti, examination of fields for diplopia) or due simply to "spastic" changes producing asymmetries of appearance with only mild, or even perhaps an absence of, exophthalmos.

Any one of these features by itself may prove misleading, for we find exceptions in everyone of these categories. But if we find combina-

tions of these various characteristics present as patterns in any given patient, the evidence grows that here we may be dealing with a potential case of "malignant exophthalmos" and we had better proceed slowly and cautiously in treating the hyperthyroidism.

The actual procedure carried out is, in general, to treat cases manifesting the above patterns with prolonged drug therapy cautiously administered if the hyperthyroidism is severe enough to warrant this. The dose of drug is altered with the changing condition of the eyes, being prepared to take measures at any point in the treatment necessary to protect them. When eye changes appear to be advancing, either the dose of the drug will be decreased or the patient will be given thyroid substance unless the hyperthyroidism is severe. The combination of severe hyperthyroidism and severe disabling exophthalmos is not very common but when it does occur it is the most difficult situation of all to control and a great threat to eye function. Occasionally there just is nothing which seems capable of arresting the relentless progress of the disease. Protection of the eyes becomes of paramount importance. It is with this small group of patients that the ophthalmologist and occasionally the neurosurgeon get their morbid impressions of the inadequacies of thyroid clinicians.

The role of administration of thyroid substance in the treatment of these patients is not clear. It is a difficult point to evaluate. It is still more a feeling than any actual evidence we have that thyroid substance helps. We have seen a number of patients, especially those with acute eye signs and symptoms, in whom there has been a fairly prompt response. This has been impressive enough so that we push thyroid in every possible case in which the eye changes appear to be progressive. But whether it is due to this, or to the caution in handling these patients, combined with the known tendency of the disease to be self-limited so that eventually the eyes become stabilized anyway, we are not certain. We do feel sure that in some of the *acute* cases the degree of proptosis is reduced (by actual careful measurements), but that the final degree of protrusion of the globe, once stability is restored, is seldom if ever less than at the beginning, and usually more even if only slightly so.

Furthermore, no one believes that there is anything specific about the action of the commonly used thyroid-inhibiting drugs in controlling exophthalmos. The important fact is that they permit a slow, reversible and controllable modification of thyroid function during the period

while the eye changes are taking place. This, it has seemed to us, has proved of considerable help in management of the eye problems for we know that the process is self-limited and that with time, patience, and careful following, the severe eye changes are not so likely to develop. Nevertheless, they have been reported in patients treated with radioactive iodine.

Whatever the virtues of one agent or method of treatment of Graves' disease as compared with another, and whatever the reasons for these associated eye changes, the internists, ophthalmologists and surgeons in our group are in essential agreement about the plan of management, based largely upon our experience with them, the main outlines of which I have attempted to delineate. We are agreed also that among the patients with Graves' disease whom we have treated during the past six years, there have been nowhere near the number of severe eye problems we saw in the groups which I have presented, and which represent our experience before the introduction of thyroid-inhibiting agents and radioactive iodine. This is not to imply that patients having this complication have not been seen by us during this interval. A fairly large number have been referred to the clinic or seen in consultation, but we have a dangerously optimistic feeling that fewer of them have been home-grown. Certainly, I can say for patients treated surgically that we have had fewer eye problems. I have a record of only one whose progressive and severe course I think we should have foreseen and forestalled during that time.

Probably the factor which is most important of all in avoiding eye trouble in Graves' disease is an *awareness* that it can and does occur (especially in patients showing any of the clinical patterns of eye changes and thyroid function I have tried to describe) so that in handling these patients we have become wary of any eye changes. We attempt to evaluate them and treat them with the cooperation and expert assistance of an ophthalmologist who follows the patients with examinations and accurate measurements throughout the course of thyroid treatment, intervening to protect the eye when indicated, whether the patient is being treated by drugs, radioactive iodine, surgery, or combinations of these methods.

After studying the individual patients in considerable detail and then the group as a whole, one comes to a point of view which may be summarized about as follows:

In Graves' disease, the train of events involving the eyes appears to be coincidental with the changes producing disturbances in thyroid function, although clinical evidence of the changes in the latter may be minimal or even lacking at the time the process begins. This train of events as it affects the eyes, however, *once started runs its course*, regardless of changes in thyroid function. Change in thyroid function produced by partial thyroidectomy, however, does appear to modify the course of these eye changes more frequently and more seriously than any other measure employed in altering thyroid function. This is most likely to occur when thyroidectomy is performed between the ages of forty to fifty-five, particularly in men. It seems likely that the stimuli which produce the thyroid change, also produce the eye change but each runs its almost independent course. In other words, changes in thyroid function from whatever form of therapy, or even "spontaneously" may modify the course of the eye changes but these appear to be quite definitely and more seriously modified or altered only by partial or subtotal thyroidectomy. Although difficult to prove, it is doubtful whether any other form of thyroid treatment so far employed actually does modify the natural course of this process.